REMARKS

Reconsideration and allowance are respectfully requested.

Claims 71-134 are pending. No new matter is added by entry of the amendment. A misspelling in claim 94 is corrected. Withdrawal of the claim objection is requested.

35 U.S.C. 112 – Definiteness

Claims 90-129 and 132-133 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

As note by the Examiner, page 7 of the specification describes the "epiK5-N,O-oversulfate" derivative as completely N-sulfated with a sulfation degree of at least 4. But she alleged that there is no higher degree of sulfation than 4. This is incorrect. Maximal degree of sulfation is 5: one sulfate group on the nitrogen and one group each on the four hydroxyls, which are present in the disaccharide. The preferred range of sulfation degree is 4 to 4.6 (see page 29 line 16, page 31 line 9, page 31 line 19, page 32 line 5, page 32 line 24, page 33 line 16, page 34 lines 8-9, page 35 lines 5-6, and page 37 line 2 of the specification) and the product of Example 4 has a sulfation degree of 4.3.

Claim 90 was directed to an epiK5-N,O-oversulfate derivative being substantially inactive for coagulation. To avoid confusion, this limitation is deleted because it is not required for patentability. Similarly, "remaining" is deleted from claim 94 because this limitation is not required for patentability.

The abbreviation "LMW" is not limited to 1500-12,000 daltons as alleged by the Examiner. On the contrary, the specification defines LMW simply as of low molecular weight. Thus, a MW from 1500 to 12,000 is LMW, but this is merely an example instead of an exclusive definition of LMW. They are obtained by fractionation or depolymerization of K5-N-sulfate and consisting of or derived from K5-N-sulfates having a mean molecular weight from approximately 1500 to approximately 12,000, calculated on a 100% N-sulfated product (see page 7 of the specification). On the other hand, the range recited in claim 103 is indicative of the molecular weight distribution.

The dependency of claim 106 is corrected. But it is unclear why the Examiner objects to claim 107 because the only moieties that are shared with claim 98 are identical: R, R' and R" are hydrogen or SO_3^-, Z is SO_3^-, and sulfation degree from 4 to 4.6.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 90-91, 93 and 132 were rejected under Section 103(a) as allegedly unpatentable over Leali et al. (J. Biol. Chem. 276:37900-37908, 2001). Applicants traverse.

The Examiner admitted that Leali does not disclose derivatives having a degree of sulfation of at least 4. But she overlooked the requirement in Applicants' claims that the N,O-oversulfate K5-polysaccharide derivative be epimerized. Instead, it was alleged that the present specification does not require that "epiK5" be an epimerized product. This is a total (and presumably deliberate) misreading of the definition bridging pages 6-7 of the specification (emphasis added):

> "epiK5" is meant the K5 and its derivatives in which 20-60% of the glucuronic units is C5-epimerized to iduronic units.

Thus, when Applicants' claims recite "epiK5" they mean (and persons skilled in the art would understand) that the K5 polysaccharide derivative **is** epimerized. No other understanding of "epiK5" is possible when the present claims are read in view of Applicants' specification and general knowledge in the art. Construing the present claims without this limitation (i.e., the K5 derivative is epimerized in 20-60% of its glucuronic units to iduronic units) is not reasonable, nor would the skilled artisan find it understandable.

Applicants submit that the rest of their disclosure is consistent with defining the claimed product as requiring epimerization of 20-60% of its glucuronic units to iduronic units. For a better understanding of the invention, the difficulty encountered by the prior art to oversulfate substrate resulting in the claimed product and Applicants' discovery of their novel reaction are discussed below.

In the present specification, Applicants teach preparing the quaternary salt of the starting epiK5-N-sulfate under the precise conditions of the claimed process (see claim 71). Thus, it is possible to obtain sulfation degrees never attained before in the prior art. In hindsight, Applicants' discovery may appear obvious after the completion of a search for a particular technical effect. But without Applicants' discovery, which was unknown to the prior art, accomplishment of the particular technical effect is only speculative and the result of wishfulness. In contrast to *Titanium Metals*, which was cited in the Office Action, this is not a close case of the prior art being "close enough" to a claimed range. The prior art did not disclose sulfation degrees higher than 4 because, simply put, the technology known on the priority date did not permit attaining such high degrees of sulfation. The maximal degree of sulfation is 5. A sulfation degree higher than 4 (e.g.,

the product of Example 4 has a degree of sulfation of 4.35) means that almost all of the available hydroxyl groups are sulfated. Thus, the difference between 3.8 (Leali) and 4.4 (Example 4) is much greater than simplistic arithmetic would indicate. In addition, in the case of such high sulfation degrees, even the common measures of sulfation degree can result in an underestimation (see the last sentence of the specification at page 46).

Therefore, the claimed invention is not obvious because the attainment of such a high sulfation degree was neither disclosed nor suggested by the prior art. Further, no evidence was provided in the Office Action of a reasonable expectation of success. The attainment of such a high degree of sulfation, neither disclosed nor suggested by the prior art, establishes that claim 71 is also not obvious and justifies the close process-intermediate-final product relationship.

Claims 90-109 and 132 were rejected under Section 103(a) as allegedly unpatentable over Casu et al. (WO 98/42754) in view of Leali et al. Applicants traverse.

Leali was discussed above. Casu at page 2, lines 10-21, refers to heparin and LMW heparin: i.e., the archetypes of anticoagulant/antithrombotic drugs, and their antithrombotic activity. When comparing heparin to LMW heparin as to their anticoagulant and antithrombotic activities, Casu refers to their inhibition of the two main factors of the coagulation cascade, Factor Xa and Factor IIa (thrombin), as well as to the global anticoagulant activity expressed by activated partial thromboplastin time (aPTT or APTT). One of ordinary skill in the art would understand that by stating that LMW heparin has a lower anticoagulant activity, Casu is referring to lower global anticoagulant (aPTT) activity. But this does not mean that LMH heparin is a glycosaminoglycan with only low anticoagulant activity. Casu's Example 6 demonstrates that products much more active than LMW heparin are also more active than oversulfated LMW heparin's inhibition of Factor Xa in the coagulation cascade. The anti-Xa and anti-IIa (antithrombin) activities actually are anticoagulant activities (see Razi et al., Biochem. J., 309:465-479, 1995; which is attached).

Leali discloses non-epimerized K5-N,O-oversulfates that do not have affinity for antithrombin III protein, which is responsible for coagulation, even though they consist of chains having the structure of the heparin precursor. As explained previously, the

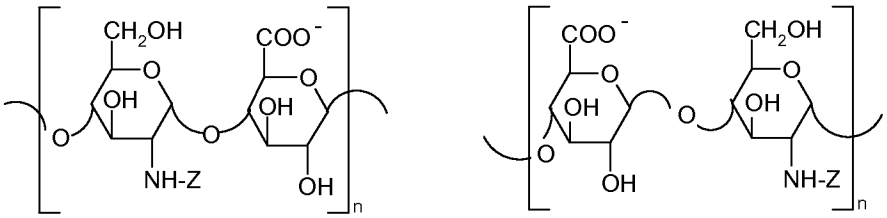
claimed epiK5-N,O-oversulfate derivatives are all epimerized. Hence, anticoagulant activity on the same order as that of Casu's products would have been expected by one of ordinary skill in the art. On the contrary, the claimed derivatives are substantially free of coagulation activity and are not antithrombotic agents. They are antiangiogenic and antiviral agents. None of these results would have been obtained with a reasonable expectation of success in the absence of evidence being provided in the Office Action.

Claims 90-109 and 132-133 were rejected under Section 103(a) as allegedly unpatentable over Casu et al. in view of Leali et al., and further in view of Oreste et al. (US 2002/0062019). Applicants traverse.

Casu and Leali were discussed above in detail. The essential features of Applicants' invention, which have been explicitly recited as limitations of the present claims, are neither taught nor made obvious by Casu and Leali. The deficiencies noted above are not addressed by citing Oreste because the Examiner herself admits that it was relied upon only for disclosure of a cosmetic composition.

On page 9 of the Office Action, it was alleged that Oreste teaches glycosaminoglycans "which have been derived from epimerized K5 polysaccharide which have been subjected to O-oversulfation and N-sulfation." This is incorrect. Oreste's abstract repeatedly teaches that oversulfation is followed by selective O-desulfation and 6-O-sulfation. No account is taken of the facts that these glycosaminoglycans have high anticoagulant and antithrombotic activity, and are useful for regulation of coagulation and thrombosis. In addition, Oreste neither discloses nor suggests, on the contrary Oreste teaches away from, epiK5-N,O-sulfates having a sulfation degree of at least 4.

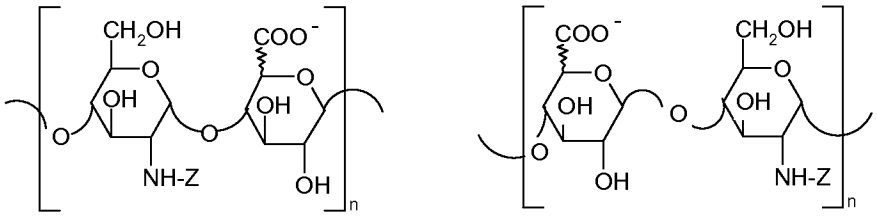
As an aid to the understanding of Applicants' invention, the following chemical structures are illustrated below. O-sulfated K5 polysaccharide products are mixtures of chains of repeating disaccharide units formed by glucuronic acid and of glucosamine linked by α-1$\rightarrow$ 4 or β-1$\rightarrow$ 4 bonds represented by formula Ia or Ib



(Ia) (Ib)

wherein Z is acetyl or sulfo (SO_3^-), and the OH groups are variously substituted with a SO_3^- group.

In the case of the claimed N,O-oversulfated K5 polysaccharide derivatives, 20-60% (normally 40-60%) of the glucuronic acid units are epimerized to iduronic acid units (group COO^- below the plane). These products may be represented by formula I'a or I'b



(I'a) (I'b)

wherein the wavy line indicates that the uronic unit may be that of glucuronic or iduronic acid, Z is a sulfo (SO_3^-) group, and the OH groups are substituted with a SO_3^- group to give a sulfation degree (also referred to as "sulphate/carboxyl ratio" or "sulphate groups per disaccharide unit") of at least 4. Applicants' claimed N,O-oversulfated K5 polysaccharide derivatives have an antiviral and/or antiangiogenetic activity, and are substantially inactive for coagulation.

Heparin may also be represented by I'a or I'b, wherein about 70% of glucuronic acid units are epimerized to iduronic acid units, Z is sulfo (SO_3^-), and the OH groups are variously substituted with a SO_3^- group to give a sulfation degree of 2-2.1. Heparin is a strong anticoagulant agent.

Thus, all of these N,O-sulfated epiK5 polysaccharide dervatives have the same skeleton (I'a) or (I'b) but their chemical and biological characteristics vary greatly as a function of the number of sulfate groups and their distribution in the skeleton.

Applicants' claimed derivatives have a degree of sulfation never attained in the prior art and, at the earliest effective filing date of this application, one of ordinary skill in the art did not have a reasonable expectation of success to increase sulfation degree of the epiK5-amine-O-oversulfate derivatives beyond a certain limit.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Double Patenting

Claims 90-109 and 132-133 were rejected as allegedly unpatentable over claims 1-13 of Patent No. 7,268,122 in view of Casu et al. Applicants traverse because their claims are patentable over the different N,O-oversulfated K5-polysaccharides claimed in the '122 patent. No improper or unjustified timewise extension of the right to exclude, or possible harassment by multiple assignees is possible unless derivatives as claimed in the present application are the only compounds that could be used in the method of treatment claimed in the '122 patent. The claims of the '122 patent also fail to teach or suggest an epimerized derivative, which is a requirement of the present claims.

Claims 90-109 and 132-133 were rejected as allegedly unpatentable over claims 1-27 of Patent No. 6,992,183 in view of Casu et al. Applicants traverse because their claims are patentable over the different N,O-oversulfated K5-polysaccharides claimed in the '183 patent. No improper or unjustified timewise extension of the right to exclude, or possible harassment by multiple assignees is possible unless derivatives as claimed in the present application are the only compounds that could be prepared in the process claimed in the '183 patent. The claims of the '183 patent also fail to teach or suggest an epimerized derivative, which is a requirement of the present claims.

Withdrawal of the double patenting rejections is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100